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(54) Title: METHOD OF SLOWING THE PROGRESSION OF HIV INFECTION

(57) Abstract

The progression of HIV infection in humans may be slowed by administering to humans suffering from such infection an agent which suppresses the endogenous production of glucocorticoids in the humans together with a replacement glucocorticoid. Ketoconazole and metyrapone are preferred agents for suppressing the endogenous production of glucocorticoids. Prednisone and dexamethasone are preferred replacement glucocorticoids, where the glucocorticoid is preferably administered in an amount less than the replacement dose. Oral administration of both the replacement glucocorticoid and glucocorticoid suppressor are preferred.

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METHOD OF SLOWING THE PROGRESSION OF HIV INFECTION

Cross-Reference to Related Application

This application is a continuation-in-part of Application Serial No. 07/996,757, filed December 24, 1992, which in turn is a continuation-in-part of Application Serial No. 07/277,161, filed November 29, 1988, now U.S. Patent No. 5,175,144, issued December 29, 1992.

Field of the Invention

This invention relates to therapeutic treatment of humans suffering from human immunodeficiency virus infection. More particularly, the invention is directed to the administration to such humans of compositions which slow the progression of such infection.

Background of the Invention

Persons infected with human immunodeficiency virus (HIV) have been described as having alterations of adrenocortical function including elevated morning plasma cortisol levels, elevated 24 hour adjusted mean plasma cortisol levels, and impaired stimulated cortisol release, when these parameters are compared with values in HIV-seronegative controls. High levels of adrenocortical stimulating hormone (ACTH) and inappropriately normal levels of ACTH in the setting of high basal cortisol levels have also been reported in HIV-infected individuals.

Evidence has been presented for the occurrence in normal subjects of a predictable diurnal peak in the number of white blood cells, number of total T lymphocytes and percentage of helper T lymphocytes. The relationships between endogenous glucocorticoids as well as exogenously administrated glucocorticoids and T lymphocyte number and subset distribution have also been described. A statistically significant decrease in both the percentage and absolute number of T helper cells (also known as CD4) four hours after a single dose of 20 milligrams of prednisone has been described.

In HIV-infected persons, loss of T helper circadian rhythms has been reported, with loss of the large-amplitude, evening peaking cycle pattern. It has been suggested, however, that at least in the early stages of disease the increases described in morning serum cortisol measurements alone may not be enough to fully explain the blunting of the CD4 rhythm. Morning cortisol values, by themselves, may not reflect the full extent of abnormal cortisol production in abnormal individuals, because of diurnal variation.

See, Malone, J.L.; Oldfield E.C.; Wagner, K.F. et al. "Abnormalities of morning cortisol levels and circadian rhythms of CD4 lymphocyte counts in human immunodeficiency virus type I-infected adult patients" *J. Inf. Dis.* **1992**, 165:185-186; Villette, J.M.; Bourin, P.; Doinel C. et al. "Circadian variations in plasma levels of hypophyseal, adrenocortical and testicular hormones in men infected with human immunodeficiency virus" *J. Clin. Endo. Metab.* **1990**, 70:572-577; Signore A.; Cugini P.; Letizia C. et al. "Study of the diurnal variation of human lymphocyte subsets" *J. Clin. Lab. Immunol.* **1985**, 17:25-28; Slade, J.D.; Hepburn, B. "Prednisone-induced alterations of circulating human lymphocyte subsets" *J. Lab. Clin. Med.* **1983**, 101:479-487; Malone J.L.; Simms, T.E.; Gray, G.C. "Sources of variability in repeated T-helper lymphocyte counts from human immunodeficiency virus type I-infected patients: total lymphocyte count fluctuations and diurnal cycle are important" *J. Acquir. Immun. Defic. Syndr.* **1990**, 3:144-151; and Murphy, B.E.P.; Dhar, V.; Ghadirian, A.M.; G. Chouinard; R. Keller "Response to Steroid Suppression in Major Depression Resistant to Antidepressant Therapy" *J. Clin. Psychopharmacol.* **1991**, 11:121-126.

Summary of the Invention

According to the present invention, human immunodeficiency virus infection in humans can be treated by a method comprising administering to a human suffering from human immunodeficiency virus infection an agent which suppresses the endogenous production of glucocorticoids together with a replacement glucocorticoid, said agent and said replacement glucocorticoid being administered in amounts which together are effective to slow the progression of the infection.

Agents believed to be useful in the present invention include drugs which reduce glucocorticoid production directly or reduce receptor binding of the glucocorticoids. Examples of such agents include opioids, such as morphine, pentazocine, nalorphine, buprenorphine, and loperamide; enkephalins and their analogs such as DAMME; sodium valproate; clonidine; ketoconazole; metyrapone; oxytocin; and mifepristone.

A preferred embodiment of the present invention is a method for treating human immunodeficiency virus infection in humans comprising administering to a human suffering from human immunodeficiency virus infection a compound selected from the group consisting of ketoconazole and metyrapone, together with a replacement glucocorticoid selected from the group consisting of prednisone and dexamethasone, said compound and said replacement glucocorticoid being administered in an amount which together are effective to slow the progression of the infection, and said replacement glucocorticoid being administered at a level less than its replacement dose level.

Another aspect of the invention is a composition for slowing the progression of HIV infection comprising a replacement glucocorticoid selected from the group consisting of prednisone and dexamethasone, in combination with an agent which suppresses the endogenous production of glucocorticoids, said agent selected from the group consisting of ketoconazole

and metyrapone, said agent and replacement glucocorticoid being present in amounts which together are effective to slow the progression of human immunodeficiency virus infection in a human suffering from said infection.

Detailed Description of the Preferred Embodiment

Glucocorticoids are corticosteroids predominantly affecting carbohydrate metabolism. Endogenous glucocorticoids influence fat and protein metabolism and have many other activities, such as affecting muscle tone and the excitation of nerve tissue and the microcirculation. In humans, the most important glucocorticoid is cortisol (hydrocortisone).

Endogenous glucocorticoids play a role in the progression of chronic renal failure. A method of retarding the progression of chronic renal failure by the use of an effective amount of an agent which suppresses the production of glucocorticoids together with an effective amount of a glucocorticoid at a dose below the replacement level is the subject of applicant's co-pending U.S. patent application Serial No. 07/996,757. The use of a glucocorticoid suppressor agent and dietary restrictions to retard the progression of chronic renal failure is the subject of applicant's U.S. Patent No. 5,175,144. However, it has not previously been suggested that suppression of the endogenous production of glucocorticoids, or blocking of their binding to receptors, may slow the progression of HIV infection.

An aspect of the present invention is a method whereby the effects of HIV infection in humans (or other animals) may be retarded by administering to humans suffering from such infection an effective amount of an agent which suppresses the daily peaks in, and total production of, glucocorticoids, together with a low dose of a replacement glucocorticoid.

Agents believed to be useful in the present invention include drugs which suppress the production of glucocorticoids. Preferably, the glucocorticoid dose

administered together with the suppressor is somewhat less than the replacement dose level. Replacement dose level is the dose that achieves an average normal level of glucocorticoid function when administered chronically to adrenalectomized subjects.

The following agents which are known to suppress glucocorticoid production in humans would appear to be useful when administered together with a glucocorticoid according to the present invention in treating, relieving the symptoms of or slowing the progression of human immunodeficiency virus infection:

(1) Ketoconazole: This is an anti-fungal agent found to inhibit adrenocortical glucocorticoid production profoundly or even completely. Farwell, A. P., *et al.*, "Total Suppression of Cortisol Excretion by Ketoconazole in the Therapy of the Ectopic Adrenocorticotropic Hormone Syndrome," Am. J. Med., 84:1063-1066 (1988). Recently, ketoconazole has been reported to prolong the half-life of the glucocorticoid prednisolone (Δ^1-hydrocortisone). B. Ulrich *et al.*, "Pharmacokinetics/Pharmacodynamics of Ketoconazole-Prednisolone Interaction," J. Pharmacol. Exp. Ther., 260:487-490 (1992). Ketoconazole is frequently used in HIV-infected individuals for treatment of systemic candidiasis.

In a previous study, conducted by the inventor, people with chronic renal failure received the combination of 400 mg of ketoconazole and 2.5 mg prednisone daily, with the result that their mean free cortisol excretion fell 43% and mean 17-OH corticosteroid excretion fell 33%.

(2) Sodium valproate: This is an anti-convulsant, widely used, but not without serious side effects and toxicity. It has been shown to reduce serum cortisol levels by more than fifty percent within a few hours in normal subjects. Aggernæs, H. *et al.*, "The Effect of Sodium Valproate on Serum Cortisol Levels in Healthy Subjects and

Depressed Patients," Acta Psychiatr. Scand., 77:170-174 (1988).

(3) Enkephalins: These pentapeptides and their synthetic analogs, notably "DAMME" ([D-ala^2, MePhe^4, Met(O)-ol] enkephalin), reduce cortisol levels acutely in man. Stubbs, W. A., *et al.*, "Hormonal and Metabolic Responses to an Enkephalin Analogue in Normal Man," Lancet, 1978:1225-1227 (December 9, 1978); and Taylor, T., "β-Endorphin Suppresses Adrenocorticotropin and Cortisol Levels in Normal Human Subjects," J. Clin. Endocrinol. Metab., 57:592-596 (1983).

(4) Opioids: Alkaloids, for example morphine, interact with the same or similar receptors as do enkephalins. Opioids shown to decrease cortisol levels in man include morphine, pentazocine, nalorphine and buprenorphine. Pende, A., *et al.*, "Evaluation of the Effects Induced by Four Opiate Drugs, with Different Affinity to Opioid Receptor Subtypes, on Anterior Pituitary LH, TSH, PRL and GH Secretion and on Cortisol Secretion in Normal Man," Biomed. Pharmacother., 40:178-182 (1986). Chronic administration of opioids may not be practical owing to side effects and/or addictive properties. However, loperamide, commercially available under the trademark "IMODIUM" from Janssen Pharmaceutica, N.V., is not addictive, but does suppress adrenocorticotrophic hormone production. See Ambrosi, B., *et al.*, "Loperamide, an Opiate Analogue, Inhibits Plasma ACTH Levels in Patients with Addison's Disease," Clin. Endocrinol., 24:483-489 (1986). Loperamide and similar butyramides are described in U.S. Patent 3,714,159 of Janssen, *et al.*

The opioid compounds of the invention are those opioid compounds which provide therapeutic benefit to a subject being administered an opioid according to the present invention. To the extent that an opioid has no accepted use in the United States, as recognized by its inclusion on Schedule I of the Controlled Substance Act (Title II, The Federal Comprehensive Drug Abuse Prevention and Control Act

(Public Law 91-513)), such opioid is not included within the scope of the invention in the United States.

(5) Clonidine: This widely used anti-hypertensive drug has recently been shown to lower cortisol levels in man. See Słowińska-Srzednicka, J., *et al.*, "Effect of Clonidine on Beta-Endorphin, ACTH and Cortisol Secretion in Essential Hypertension and Obesity," Eur. J. Clin. Pharmacol., 35:115-121 (1988); and Lechin, F., *et al.* "Role of Stress in the Exacerbation of Chronic Illness: Effects of Clonidine Administration on Blood Pressure and Plasma Norepinephrine, Cortisol, Growth Hormone and Prolactin Concentrations," Psychoneuroendocrinology, 12:117-129 (1987).

(6) Oxytocin: Intravenous infusion of this hormone (widely used to induce labor) lowers cortisol levels in normal men. Legros, J. J., *et al.*, "Confirmation of the Inhibitory Influence of Exogenous Oxytocin on Cortisol and ACTH in Man: Evidence of Reproducibility," Acta Endocrinol., 114:345-349 (1987). Oxytocin can be given as an intranasal spray, and side effects are minor.

(7) Mifepristone: Also known as RU486 or RU38486, available from Roussel-Uclaf. This new hormone analog blocks glucocorticoid receptors and has been used to treat hyperadrenocorticism (Cushing's syndrome). Bertagna, X., *et al.*, "The New Steroid Analog RU 486 Inhibits Glucocorticoid Action in Man," J. Clin. Endocrinol. Metab., 59:25-28 (1984); Moguilewsky, M., *et al.*, "RU 38486: Potent Antiglucocorticoid Activity Correlated with Strong Binding to the Cytosolic Glucocorticoid Receptor Followed by Impaired Activation," J. Steroid Biochem., 20:271-6 (1984); Gagne, D., et al., "RU 38486: A Potent Antiglucocorticoid *In Vitro* and *In Vivo*," J. Steroid Biochem., 23:247-251 (1985); and Teutsch, G., *et al.*, "17α-Alkynyl-11β,17-Dihydroxyandrostane Derivatives: A New Class of Potent Glucocorticoids," Steroids, 38:651-665 (1981). Mifepristone also reduces protein catabolism in acutely uremic rats. Schaefer, R. M., *et al.*, "Evidence for Reduced Catabolism by the Antiglucocorticoid RU 38486 in

Acutely Uremic Rats," Am. J. Nephrol., 7:127-131 (1987). Single doses induce abortion, and chronic use induces a state of hypoadrenocorticism, but the problem is how to evaluate glucocorticoid function when the receptors are blocked. Nieman, L. K., *et al.*, "Clinical Applications of the Glucocorticoid and Progestin Antagonist RU 486," Agarwal, M.K., editor, Receptor Mediated Antisteroid Action, de Gruyter, Berlin, New York (1987).

(8) Metyrapone: This steroid suppressive drug has been successfully used in the treatment of major depression. See Murphy, B.E.P., "Treatment of Major Depression with Steroid Suppressive Drugs," J. Steroid Biochem. Molec. Biol., 39(2):239-244 (1991) and references cited therein. This medicinal agent has also been used in the long-term management of humans afflicted with pituitary-dependent bilateral adrenal hyperplasia (Cushing's disease). See Jeffcoate, W. J., *et al.*, "Metyrapone in Long-Term Management of Cushing's Disease," British Medical Journal, 2:215-217 (1977) and references cited therein.

Glucocorticoids are steroid hormones which modify certain metabolic reactions and have an anti-inflammatory effect. Endogenous glucocorticoids are produced by the adrenal cortex and influence carbohydrate, fat and protein metabolism and are also known to affect muscle tissue, the nervous system and the circulatory system. Glucocorticoids produced by the human adrenal gland include cortisol, corticosterone, 11-deoxycortisol, 11-deoxycorticosterone, aldosterone, 18-hydroxycorticosterone and 18-hydroxy, 11-deoxycorticosterone. In humans, cortisol (also known as hydrocortisone) is the most abundantly produced. Many analogs of hydrocortisone, such as prednisone (Δ^1-dehydrocortisone), prednisolone (Δ^1-hydrocortisone) and dexamethasone (16α-methyl-9α-fluoro-Δ^1-hydrocortisone) are available commercially.

Endogenous glucocorticoids play a role in the progression of chronic renal failure. U.S. Patent No.

5,175,144 discloses that suppression of the endogenous production of glucocorticoids or blocking of their binding to receptors slows or arrests the progression of chronic renal failure. While not wishing to be bound by any particular theory, ketoconazole, in particular, may slow progression of HIV infection by suppression of diurnal cortisol peaks or by exerting an antioxidant effect, either of which may underlie the relief of the symptoms of HIV infection anticipated when HIV-infected individuals are provided with the method of treatment of the invention.

According to the present invention, it is expected that administration of a glucocorticoid suppressor together with a replacement glucocorticoid is more effective than administration of a suppressor alone in retarding or arresting the progression HIV infection. Suppression of glucocorticoid action through suppression of production entails the possibility of excessive suppression, thereby causing glucocorticoid insufficiency. In the present invention, a glucocorticoid suppressor is administered together with a glucocorticoid where, preferably, the dose of glucocorticoid is chosen to be somewhat less than the "replacement dose level." Thus, if the suppressor were totally effective in suppressing adrenocortical production of glucocorticoids, and if it had no effects on glucocorticoid metabolism or on glucocorticoid interaction with the glucocorticoid receptors, a low level of glucocorticoid function would still be present.

Furthermore, when a glucocorticoid suppressor such as metyrapone is given, a compensatory increase occurs in the secretion of adrenocorticotrophic hormone, owing to release from feedback inhibition by cortisol. Giving a replacement glucocorticoid simultaneously prevents this "escape" phenomenon, which otherwise can overcome drug-induced suppression of glucocorticoid production.

Administration can be oral or parenteral. The appropriate dosages of the glucocorticoid suppressor can be readily ascertained from the scientific literature cited

herein and by routine experimentation. For example, with respect to ketoconazole, appropriate dosages are discussed in Farwell *et al.*, supra. A dosage of 200-400 mg/day suppresses glucocorticoid production to a mild degree.

Aggernæs *et al.*, supra, discloses that an 800 mg dosage of sodium valproate administered by intravenous injection suppressed serum cortisol levels in normal subjects. According to the Physicians' Desk Reference, 44th Edition, pp. 513-515 (1990), the usual daily dose of valproate is 10 mg/kg/daily and the maximum recommended dosage is 60 mg/kg/daily.

With regard to enkephalins, appropriate dosages for use in conjunction with the present methods are suggested in Stubbs *et al.*, supra, and Taylor, supra.

The only known opioid which may be administered on a long-term basis without danger of addiction is loperamide. Concurrent use of a laxative would be required. According to Ambrosi *et al.*, supra, an oral dosage of 16 mg produced a decrease in plasma adrenocorticotropic hormone levels. According to the Physicians' Desk Reference, supra, at pp. 1083-1084, the daily dosage of loperamide should not exceed 16 mg.

A daily dosage of clonidine ranging from 0.2 mg-0.6 mg suppresses cortisol levels as discussed in Słowińska-Srzednicka *et al.*, supra, and Lechin *et al.*, supra.

Appropriate dosages of oxytocin are suggested in Legros *et al.*, supra.

A suitable dosage of metyrapone is from about 0.25 g twice daily to about 1.0 g four times daily, as discussed in Jeffcoate *et al.*, supra, and Murphy supra.

A suitable dosage of prednisone is from about 2.5 mg/day to about 60 mg/day, as discussed in the Physicians' Desk Reference, 48th Edition, pp. 2407-2409. A dosage of about 2.5 mg/day is preferred.

A suitable dosage of dexamethasone is from about 0.1 mg/day to about 9 mg/day, as discussed in the Physicians' Desk

Reference, 48th Edition, pp. 1429-1431. A dosage of about 0.1 mg/day is preferred.

Preferably, in the method and composition of the present invention, the glucocorticoid suppressor is ketoconazole and the glucocorticoid is prednisone. In another preferred embodiment of the invention, the glucocorticoid suppressor is metyrapone and the glucocorticoid is prednisone. In still another preferred embodiment, the glucocorticoid suppressor is ketoconazole and the glucocorticoid is dexamethasone. A given dose of prednisone exerts a greater glucocorticoid effect in the presence of ketoconazole. The more slowly ketoconazole is metabolized in a given patient (thereby causing relatively more adrenocortical suppression), the more slowly prednisone will be metabolized, thus overcoming possible glucocorticoid insufficiency. This combination of drugs tends to "clamp" glucocorticoid function at a low, but adequate, level preventing glucocorticoid insufficiency.

Another possible benefit of the glucocorticoid clamp of the method of the present invention is that diurnal variations in glucocorticoid levels are blunted or eliminated. These variations are about five-fold in normal subjects, but their function, if any, is unknown. While not wishing to be bound by any particular theory, the peaks of glucocorticoid levels during each day, as well as peaks occurring from day to day in response to various stimuli including stress, may promote the ill-effects of HIV infection. It is known that sustained high levels of glucocorticoids impair healing. See S. Matsusue *et al.*, "Healing of Intestinal Anastomoses in Adrenalectomized Rats Given Corticosterone," Am. J. Physiol., 263:R164-R168 (1992).

Additionally, high levels of glucocorticoid production have been observed in males infected with the human immunodeficiency virus (HIV). Excessive glucocorticoid production was observed in both HIV-positive and early AIDS individuals. These high levels may contribute to the

progressive decline in T helper lymphocyte observed in HIV-infected individuals. See J.M. Villette *et al.*, "Circadian Variations in Plasma Levels of Hypophyseal, Adrenocortical and Testicular Hormones in Men Infected with Human Immunodeficiency Virus," J. Clin. Endocrinol. Metab., 70:572-577 (1990).

In order to demonstrate the effect of the administration of agents which suppress glucocorticoid action together with a glucocorticoid, a clinical study is to be conducted as described below.

Clinical Test Methods

A double-blind, placebo-controlled, randomized study was designed to study 40 HIV-infected individuals who are asymptomatic or mildly symptomatic with a CD4 count percentage equal to or greater than 15%. Twenty subjects are randomly assigned to receive the placebo and twenty subjects are randomly assigned to receive the study drug combination. Subjects undergo two determinations of CD4 percentage and counts prior to initiation of treatment. At baseline, two weeks, four weeks, and eight weeks into treatment, subjects are admitted for inpatient hospital stays for the purpose of collecting twenty-four hour urine specimens..

The group receiving drug treatment according to the invention receive a daily dosage of 400 mg ketoconazole and 2.5 mg prednisone.

A causal relationship between relief of the symptoms of HIV infection and administration of a glucocorticoid suppressor together with a glucocorticoid in patients with HIV infection is anticipated from the data obtained from this study. Therefore, it is believed that other agents and measures that suppress the production of glucocorticoids administered together with a dose of prednisone or another glucocorticoid should provide treatment or relief for the symptoms of HIV infection.

The present invention may be embodied in other specific forms without departing from the spirit or essential

attributes thereof and, accordingly, reference should be made to the appended claims, rather than to the foregoing specification as indicating the scope of the invention.

CLAIMS

1. A method for treating human immunodeficiency virus infection in humans comprising administering to a human suffering from human immunodeficiency virus infection an agent which suppresses the endogenous production of glucocorticoids together with a replacement glucocorticoid, said agent and said replacement glucocorticoid being administered in amounts which together are effective to slow the progression of the infection.

2. The method according to claim 1, wherein the agent which suppresses the endogenous production of glucocorticoids and the replacement glucocorticoid are administered orally.

3. The method according to claim 1, wherein the agent which suppresses the endogenous production of glucocorticoids is selected from the group consisting of ketoconazole, metyrapone, sodium valproate, enkephalins and their synthetic analogs, opioids, clonidine and oxytocin.

4. The method of claim 1, wherein the effective amount of the replacement glucocorticoid is less than its replacement dose level.

5. The method according to claim 1, wherein the agent which suppresses the endogenous production of glucocorticoids is ketoconazole.

6. The method of claim 5, wherein the ketoconazole is administered in an amount of about 200 to about 400 mg/day.

7. The method according to claim 1, wherein the agent which suppresses the endogenous production of glucocorticoids is metyrapone.

8. The method according to claim 7, wherein the metyrapone is administered in an amount of about 500 to 4,000 mg/day.

9. The method according to claim 1, wherein the replacement glucocorticoid is prednisone.

10. The method of claim 9, wherein the prednisone is administered in an amount of about 2.5 mg/day.

11. The method according to claim 1, wherein the replacement glucocorticoid is dexamethasone.

12. The method of claim 11, wherein the dexamethasone is administered in an amount of about 0.1 mg/day.

13. A method for treating human immunodeficiency virus infection in humans comprising administering to a human suffering from human immunodeficiency virus infection a compound selected from the group consisting of ketoconazole and metyrapone, together with a replacement glucocorticoid selected from the group consisting of prednisone and dexamethasone, said compound and said replacement glucocorticoid being administered in an amount which together are effective to slow the progression of the infection, and said replacement glucocorticoid being administered at a level less than its replacement dose level.

14. The method according to claim 13, wherein the compound is ketoconazole, said compound being administered in an amount of about 200 to 400 mg/day, and the replacement glucocorticoid is prednisone, said replacement glucocorticoid being administered in an amount of about 2.5 mg/day.

15. The method according to claim 13 wherein the compound is metyrapone, said compound being administered in an amount of about 500 to about 4,000 mg/day, and the replacement glucocorticoid is prednisone, said replacement glucocorticoid being administered in an amount of about 2.5 mg/day.

16. The method according to claim 13 wherein the compound is ketoconazole, said compound being administered in an amount of about 200 to 400 mg/day, and the replacement glucocorticoid is dexamethasone, said replacement glucocorticoid being administered in an amount of about 0.1 mg/day.

17. The method according to claim 13, wherein the compound and the replacement glucocorticoid are administered orally.

18. A composition for slowing the progression of HIV infection comprising a replacement glucocorticoid selected from the group consisting of prednisone and dexamethasone, in combination with an agent which suppresses the endogenous production of glucocorticoids, said agent selected from the group consisting of ketoconazole and metyrapone, said agent and replacement glucocorticoid being present in amounts which together are effective to slow the progression of human immunodeficiency virus infection in a human suffering from said infection.

19. The composition according to claim 18 wherein the replacement glucocorticoid is present in less than its replacement dose.

20. The composition according to claim 18 comprising prednisone and ketoconazole.

21. The composition according to claim 18 comprising prednisone and metyrapone.

22. The composition according to claim 18 comprising dexamethasone and ketoconazole.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/05662

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/495, 31/50
US CL :514/252
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/171, 179, 332

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN - compound & antiviral methods of use

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, VOLUME 80, NO. 9 ISSUED 30 AUGUST 1971, COLMANO ET AL., "EFFECT OF METYRAPONE AND DDD (DICHLORO DIPHENYLDICHLOROETHANE) ON INFECTIOUS DISEASES", ABSTRACT NO. 60521d, POULTRY SCI., 1971, 50(3), 850-54, SEE ENTIRE DOCUMENT.	1-22
Y	CHEMICAL ABSTRACTS, VOLUME 103, NO. 23 ISSUED 09 DECEMBER 1985, POTTAGE ET AL., "INHIBITION OF IN-VITRO HBsAg PRODUCTION BY AMPHOTERICIN B AND KETOCONOZOLE" ABSTRACT NO. 189241p, J. MED. VIROL., 1985, 16(3), 275-81, SEE ENTIRE DOCUMENT.	1-22

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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Date of the actual completion of the international search
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International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, VOLUME 105, NO. 13 ISSUED 29 SEPTEMBER 1986, POTTAGE ET AL., "IN-VITRO ACTIVITY OF KETOCONAZOLE AGAINST HERPES SIMPLEX VIRUS", ABSTRACT NO. 108012f, ANTIMICROB. AGENTS CHEMOTHER., 1986, 30(2), 215-19, SEE ENTIRE DOCUMENT.	1-22
Y	MEDLINE, VOLUME 88, ISSUED 1988, RUBINSTEIN ET AL.; "CORTICOSTEROID TREATMENT FOR PULMONARY LYMPHOID HYPERPLASIA IN CHILDREN WITH ACQUIRED IMMUNE DEFICIENCY SYNDROME" ABSTRACT NO. 88143818, PEDIATRICS PULMONOL, 1988, 4(1), 13-17, SEE ENTIRE DOCUMENT.	1-22